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添付公開書類
国際調査報告書

(54)Title: **METHODS FOR MAKING HARDLY SOLUBLE MEDICINE AMORPHOUS**

(54)発明の名称 難溶性薬物の非晶質化法

(57) **Abstract**

A process for preparing a solid dispersion of a hardly soluble medicine which comprises heating the hardly soluble medicine, an amorphism-inducing agent and an amorphism stabilizer or mechanochemically treating the same; and a process for producing a solid dispersion of a hardly soluble medicine which comprises high-frequency heating the hardly soluble medicine and an amorphism stabilizer. These processes make it possible to make hardly soluble medicines amorphous at a temperature lower than those employed in the conventional methods. The solid dispersions of the amorphous hardly soluble medicines thus obtained have an improved mucosal or rectal adsorption rate, which makes it possible to elevate their bioavailability.

（５７）要約

難溶性薬物と非晶質化誘導剤及び非晶質安定化剤とを、加熱又はメカノケミカル処理することを特徴とする難溶性薬物の固体分散体の製造方法；並びに

難溶性薬物と非晶質安定化剤を、高周波加熱することを特徴とする難溶性薬物の固体分散体の製造方法。

これらの製造方法により、従来より低い温度で難溶性薬物の非晶質化が可能になり、得られた非晶質化された難溶性薬物の固体分散体の粘膜又は直腸からの吸収効率が改善され、生物学的利用能を高めることができる。

明 細 書

難溶性薬物の非晶質化法

技術分野

本発明は、難溶性薬物を有効に利用する技術、特に新規な非晶質化法による固体分散体の製造法に関する。この技術は、薬物の溶出性が課題とされる分野、例えば農薬、香粧品や医療分野、特に医療分野にて利用される。

背景技術

経口投与製剤の設計において、難溶性薬物の溶解性や吸収性を改善させることにより生物学的利用能を高めることが、薬剤の有効性、安全性面の点で重要である。

難溶性薬物の生物学的利用能を高める方策として、薬物の粒子の微粒化と濡れや分散性の改善、固体分散体化、多形の利用などによる薬剤の溶解性を改善する方法があるが、特に注目される方法は、薬物の非晶質化法による固体分散体を製造する方法である。固体分散体とは、薬物を担体中に単分子状態で分散させたもので、薬物が完全に非晶質化した状態で保持された分散体を示す。一般に非晶質形は、結晶形に比較して、高エネルギー状態にあり、高い溶解性が期待されるものである。

固体分散体の製造法は、溶媒法、溶融法（加熱法）、溶融－溶媒法、メカノケミカル法、その他に大別される。

溶媒法は、薬物と非晶質安定化剤である水溶性高分子基剤の両者を溶解する有機溶媒に溶解せしめた後に、核粒子の存在下又はそのままの状態で、溶媒を留去・気散せしめて固体分散体を得る方法である。この方法は、難溶性薬物の溶解性

を改善させる方法としては優れた方法ではあるが、大量の有機溶媒を使用することから、製造コストが高く、又薬剤への残存溶媒が懸念される例も見られるなど欠点がある。

溶融法（加熱法）は、薬物と非晶質安定化剤である水溶性高分子基剤の混合物の融点降下を利用し、両者の融点以下で加熱混練し、薬物を分子状態で分散させ、冷却、固化、粉砕する方法である。

溶融法は、有機溶媒を使用しないという点で優れたものである。しかし、難溶性薬物の種類によっては、固定分散体用担体としての非晶質化安定剤の添加のみでは、十分な非晶質化が得られないことがある。

又、薬物を完全に非晶質化させるためには、薬物や固定分散体用担体の融点以下ではあるが、高温で混練処理する必要があり、薬物の分解、担体の劣化などがみられるのみならず、非晶質化が不十分な例も生じる。

例えば、難溶性薬物と非晶質安定化剤である水溶性高分子基剤のみを用いて融点降下を利用して両者を加熱溶融する方法では、融点降下はたかだか１０℃程度であり、熱処理温度が高温となるばかりか、高分子基剤はもともと非晶質であることが多いため、見かけの溶融粘度が高く、薬物と水溶性高分子のミクロ分散性が悪く、薬物によっては、十分な非晶質化が得られないこともある。

又、固体分散体用担体として、水溶性高分子基剤ではなく、非晶質化誘導剤としてのホスファチジルコリンなどの低分子化合物を用い、難溶性薬物と加熱溶融する試みもなされている。しかし、加熱処理により薬物の分解変成等が起こることが懸念される。又、加熱処理品を室温まで温度を下げた場合、得られた非晶質状態が保持されにくく、安定性が悪いことが懸念される。

メカノケミカル法（処理）は、圧縮、剪断、摩擦などの機械エネルギーを用いて薬物固体の非晶質化の促進、非晶質化した薬物の担体への分散促進を向上させ、固体分散体を得る方法である。具体的には、ボールミル混合粉砕、遊星ミル処理、

圧縮プレス処理、剪断ロール混合処理等の処理等がある。

メカノケミカル処理では、難溶性薬物に非晶質安定化剤を加えた場合であっても、機械エネルギーのレベルが低いためか、単独では完全に非晶質化することは難しく、特殊な器械が必要とされる場合もある（特開平４－８１８１０６）。

以上のように、従来の方法より安価で完全な非晶質化状態の固体分散体を、工業的に安価に得られる方法が求められている。

発明の開示

本発明者らは、これら従来法に残された課題を克服すべく、鋭意検討した結果、（１）難溶性薬物、（２）非晶質化誘導剤及び（３）非晶質安定化剤の３成分を混合し、加熱又はメカノケミカル処理することを特徴とする難溶性薬物の非晶質化法を見出した。又、加熱処理として、通常のヒーター加熱やスチーム加熱より高周波加熱が好ましいことを見出したものである。

又、（１）難溶性薬物及び（３）非晶質安定化剤の２成分を混合し、高周波加熱することを特徴とする難溶性薬物の非晶質化法を見出したものである。

さらに本発明の非晶質化法により得られた固体分散体を用いた難溶性薬物の製剤の製造も可能である。

本発明における（１）難溶性薬物は、水に対する溶解度が極めて低く、腸管、鼻粘膜、直腸等からの吸収性の悪い薬物であって、通常の製剤化では吸収性の改善が困難な薬物であり、非晶質化することにより吸収を高めることができる薬物である。例えば、ニフェジピン、塩酸ニカルジピン等のジヒドロピリジン系の化合物、フェナセチン、ジギトキシン、ジアゼパム、フェニトイン、トルブタミド、テオフィリン、グリセオフルビン、クロラムフェニコールなどが挙げられる。

本発明における（２）非晶質化誘導剤は、薬物との混合物が融点降下を起こす化合物であれば良く、特に結晶性化合物が好ましい。熱又は機械エネルギー存在

下で、難溶性薬物の結晶格子エネルギーを低エネルギー方向に変化させ、かつ、同一温度にて結晶格子のゆらぎを大きくする機能・性質を持つ化合物である。難溶性薬物の種類に応じて選択される非晶質化誘導剤が異なり、例えば、a)塩基性難溶性薬物の場合は、中性物質又は酸性物質、特に酸性物質、b)酸性難溶性薬物の場合は、中性物質又は塩基性物質、特に塩基性物質を選択することが好ましい。

非晶質化誘導剤は、具体的には例えば、アミノ酸又はその塩（アスパラギン酸とそのNa塩、Mg塩等、グリシン、アラニン、グルタミン酸類及び塩酸グルタミン酸等）、アスパラテーム、エリソルビン酸又はその塩（Na塩等）、アスコルビン酸又はその塩（Na塩等）、ステアリン酸エステル、アミノエチルスルホン酸、イノシトール、エチル尿素、クエン酸又はその塩（三Na、二Na、二水素Na等の塩、Ca塩等）、グリチルリチン酸又はその塩（三Na、二Na等のNa塩、二アンモニウム、モノアンモニウム等のアンモニウム塩、K塩等）、グルコン酸又はその塩（Na塩、Ca塩、Mg塩等）、クレアチニン、サリチル酸又はその塩（Na塩等）、酒石酸又はその塩（Na塩、K・Na塩、水素・K塩等）、コハク酸又はその塩（二Na、一Na等のNa塩）、酢酸カルシウム、サッカリンナトリウム、水酸化アルミニウム、ソルビン酸又はその塩　（K塩等）、デヒドロ酢酸又はその塩（Na塩等）、チオリンゴ酸ナトリウム、ニコチン酸アミド、尿素、フマル酸又はその塩（Na塩等）、マクロゴール類、マルトース、マルトール、マレイン酸、マンニトール、メグルミン、デスオキシコール酸ナトリウム及びホスファチジルコリン等が挙げられる。

好ましくは、非晶質化誘導剤は、アミノ酸又はその塩（アスパラギン酸とそのNa塩,Mg塩等、グリシン、アラニン、グルタミン酸類及び塩酸グルタミン酸等）、アスコルビン酸又はその塩（Na塩等）、ステアリン酸エステル、アミノエチルスルホン酸、エチル尿素、クエン酸又はその塩（三Na、二Na、二水素Na等の塩、Ca塩等）、グリチルリチン酸又はその塩（三Na、二Na等のNa塩、二アンモニウム、モノアンモニウム等のアンモニウム塩、K塩等）、クレアチニン、酒石酸又はそ

の塩（Na塩、K・Na塩、水素・K塩等）、コハク酸又はその塩（二Na、一Na等のNa塩）、尿素、フマル酸又はその塩（Na塩等）、マクロゴール類、マルトース、マルトール、マンニトール及びメグルミン等が挙げられる。

さらに好ましくは、非晶質化誘導剤は、アミノ酸又はその塩（アスパラギン酸とそのNa塩,Mg塩等、グリシン、アラニン、グルタミン酸類及び塩酸グルタミン酸等）、エチル尿素、グリチルリチン酸又はその塩（三Na、二Na等のNa塩、二アンモニウム、モノアンモニウム等のアンモニウム塩、K塩等）、酒石酸又はその塩（Na塩、K・Na塩、水素・K塩等）、コハク酸又はその塩（二Na、一Na等のNa塩）、尿素、マルトース、マルトール、マンニトール及びメグルミン等が挙げられる。

より好ましくは、非晶質化誘導剤は、グリチルリチン酸又はその塩（三Na、二Na等のNa塩、二アンモニウム、モノアンモニウム等のアンモニウム塩、K塩等）、コハク酸又はその塩（二Na、一Na等のNa塩）、尿素、マルトール及びマンニトール等が挙げられる。

又、非晶質誘導化剤と難溶性薬物との混合物の融点降下は難溶性薬物との組み合わせにより異なるが、好ましくは難溶性薬物の融点より５℃以上低下させる化合物を用いるのがよい。

さらに好ましくは、非晶質誘導化剤と難溶性薬物との混合物の融点降下が難溶性薬物の融点より１５℃以上、特に好ましくは２５℃以上低下させる化合物を用いるのがよい。

加熱が高周波加熱の場合、非晶質化誘導剤を用いずに難溶性薬物と非晶質化安定剤のみの混合物を高周波加熱することにより難溶性薬物の非晶質化が可能である。当然、非晶質化誘導剤を配合した３成分系の高周波加熱も充分の結果を与える。

非晶質安定化剤は、難溶性薬物の結晶構造を非晶質化誘導剤でゆるがせた上で、

その結晶格子の変揺状態に相互作用して非晶質状態を安定化するものである。

従って、上記作用を持つ非晶質安定化剤であれば、本発明に用いることができる。すなわち難溶性薬物と相互作用を持つ官能基を保持する化合物であれば非晶質安定化剤はいずれでも良いが、好ましくは難溶性薬物と相溶性の高い、フレキシブルな官能基を持つ、熱安定性の高い化合物、例えば下記の非晶質性の高分子基剤を用いるのがよい。難溶性薬物との相溶性が高い化合物とは両者の溶解性パラメーター（Solubility Parameter:ENCYCLOPEDIA OF POLYMER SCIENCE AND ENGINEERING, VOL.15 P393, JOHN WILEY & SONS, INC. 1989）が近い値の化合物である。さらに好ましくは、非晶質化安定剤は難溶性薬物だけでなく非晶質化誘導剤とも相溶性が高い化合物である。

又、難溶性薬物の種類に応じて選択される相互作用する非晶質化安定剤の官能基が異なり、例えば、a)塩基性難溶性薬物の場合は、中性物質又は酸性物質、特に酸性物質、b)酸性難溶性薬物の場合は、中性物質又は塩基性物質、特に塩基性物質を選択することが好ましい。

本発明における（３）非晶質安定化剤としては、例えば、セルロース誘導体（例えば、ヒドロキシエチルセルロース、ヒドロキシプロピルメチルセルロース（ＨＰＭＣ）、ヒドロキシプロピルセルロース（ＨＰＣ）、ヒドロキシプロピルメチルセルロースアセテートサクシネート（ＨＰＭＣ－ＡＳ）、メチルセルロース、エチルセルロース、カルボキシメチルセルロース、酢酸フタル酸セルロース等が挙げられる）、ポリビニルピロリドン、架橋ポリビニルピロリドン、ポリビニルアルコール、ポリ酢酸ビニル、ビニルアルコール・酢酸ビニルコポリマー、エチレン・酢酸ビニルコポリマー、ポリエチレンオキサイド誘導体（例えば、ポリエチレングリコール、ポリオキシエチレンポリオキシプロピレンセチルエーテル、ポリオキシエチレンアルキルエーテル、ポリオキシエチレンオクチルフェニルエーテル、ポリオキシエチレンオレイルアミン、ポリオキシエチレンオレイル

エーテル、ポリオキシエチレンオレイルエーテルリン酸ナトリウム、ポリオキシエチレン硬化ヒマシ油、ポリオキシエチレンステアリルエーテル、ポリオキシエチレンステアリルエーテルリン酸、ポリオキシエチレンセチルエーテル、ポリオキシエチレンセチルエーテルリン酸ナトリウム、ポリオキシエチレンソルビットミツロウ、ポリオキシエチレンノニルフェニルエーテル、ポリオキシエチレンヒマシ油、ポリオキシエチレンベヘニルエーテル、ポリオキシエチレンポリオキシプロピレングリコール、ポリオキシエチレンポリオキシプロピレンセチルエーテル、ポリオキシエチレンラウリルエーテル、ポリオキシエチレンラノリン、ポリソルベート４０、ポリソルベート６０、ポリソルベート６５、ポリソルベート８０等が挙げられる）、ポリスチレンスルホン酸ナトリウム、ゼラチン、可溶性デンプン、プルラン、デキストラン、アラビアゴム、コンドロイチン硫酸又はそのNa塩、ヒアルロン酸、ペクチン、キチン、キトサン、α、β又はγ－シクロデキストリン、アルギン酸誘導体（アルギン酸及びそのNa塩及びプロピレングリコールエステル等が挙げられる）、アクリル樹脂類（メタアクリル酸、メタアクリル酸メチル、メタアクリル酸ブチル、メタアクリル酸ジメチルアミノエチル、メタアクリル酸塩化トリメチルアンモニウムエチル、アクリル酸、アクリル酸エチル等のメタアクリル酸誘導体及び／又はアクリル酸誘導体のホモポリマー又はコポリマー等、例えばアミノアルキル・メタアクリレートコポリマー、メタアクリル酸メチル・メタアクリル酸コポリマー、メタアクリル酸・アクリル酸エチルコポリマー、メタアクリル酸・アクリル酸n-ブチルコポリマー、アクリル酸エステル・酢酸ビニルコポリマー、アクリル酸-2-エチルヘキシル・ビニルピロリドンコポリマー、アクリル酸デンプン等が挙げられる）及びポリビニルアセタールジエチルアミノアセテート等を挙げることができる。

その他、ゲル形成能を有する化合物、例えば、二酸化ケイ素、水酸化アルミニウム等も本発明の非晶質安定化剤として用いることができる。

好ましくは、非晶質安定化剤として、ヒドロキシエチルセルロース、ヒドロキシプロピルメチルセルロース（HPMC）、ヒドロキシプロピルセルロース（HPC）、ヒドロキシプロピルメチルセルロースアセテートサクシネート（HPMC－AS）、ポリビニルピロリドン、ポリスチレンスルホン酸ナトリウム、デキストラン、α、β又はγ－シクロデキストリン、アクリル樹脂類（メタアクリル酸、メタアクリル酸メチル、メタアクリル酸ブチル、メタアクリル酸ジメチルアミノエチル、メタアクリル酸塩化トリメチルアンモニウムエチル、アクリル酸、アクリル酸エチル等のメタアクリル酸誘導体及び／又はアクリル酸誘導体のホモポリマー又はコポリマー等が挙げられる）及びポリビニルアセタールジエチルアミノアセテート等を挙げることができる。

より好ましくは、非晶質安定化剤として、ヒドロキシプロピルメチルセルロース（HPMC）、ヒドロキシプロピルメチルセルロースアセテートサクシネート（HPMC－AS）、ポリビニルピロリドン、アクリル樹脂類（メタアクリル酸、メタアクリル酸メチル、メタアクリル酸ブチル、メタアクリル酸ジメチルアミノエチル、メタアクリル酸塩化トリメチルアンモニウムエチル、アクリル酸、アクリル酸エチル等のメタアクリル酸誘導体及び／又はアクリル酸誘導体のホモポリマー又はコポリマー等が挙げられる）及びポリビニルアセタールジエチルアミノアセテート等を挙げることができる。

本発明における（1）難溶性薬物、（2）非晶質化誘導体及び（3）非晶質安定化剤の配合種類及び比率は、使用される難溶性薬物の種類により適宜選定されるが、通常重量比で、（1）：（2）：（3）＝1：（0．1－10）：（0．1－10）であり、好ましくは、（1）：（2）：（3）＝1：（0．3－3）：（0．3－8）、さらに好ましくは、（1）：（2）：（3）＝1：（0．3－2）：（0．5－5）である。

本発明の難溶性薬物の固体分散体は、必須成分の（１）難溶性薬物、（２）非晶質化誘導剤及び（３）非晶質安定化剤を、湿式又は乾式にて造粒（混合）し、その混合物を混合と同時に又は混合後、非晶質化誘導開始温度以上でかつ難溶性薬物が分解劣化しない温度にて熱処理するか、又はこの加熱処理と同一のエネルギー条件のメカノケミカル処理することにより得られる。この時の混合物の加熱温度は難溶性薬物の融点以下で行うのが好ましく、可能な限り非晶質化誘導開始温度に近い温度が好ましい。加熱温度が非晶質化誘導開始温度より例えば５ないし１０℃以上低いと非晶質化が充分に進行しない。

非晶質化誘導開始温度とは、難溶性薬物と非晶質化誘導剤の混合試料（１：１）１０ｍｇを、示差走査熱量計（ＤＳＣ）を用いて、昇温速度１０℃／分で測定する時に観察される吸熱開始温度（ピーク立ち上がり温度）をいう。

造粒（混合）方法としては、特別な手法は必要なく、万能混合機、流動造粒装置、ダッシュミル、湿式造粒機、乾式造粒機等が用いられる。又造粒時に熱処理を行ってもよく、造粒後、通常のヒーター加熱、スチーム加熱、赤外線加熱や遠赤外線加熱等の加熱方法にて、例えば、棚式乾燥機、流動層乾燥機、ジャイロ乾燥機、粉体乾燥機等で加熱処理をして非晶質化を行ってもよい。

さらに、加えるエネルギーとしては、熱のみならず、圧縮、剪断、摩擦等の機械エネルギーによるメカノケミカル処理にても、非晶質化は可能である。例えば、前述必須３成分を加熱せずに、ボールミル粉砕、遊星ミル処理、圧縮プレス処理、剪断ロール処理、ニーダー等の処理等のメカノケミカル処理のみによっても非晶質化は可能である。この方法によれば、熱に対し不安定な薬物に対しても非晶質化が可能になる。

加えて、超音波などの振動エネルギーや電場、磁気等の電磁気エネルギー処理にて、３成分混合系中の難溶性薬物の結晶格子の変揺状態化エネルギーとして用いることも可能である。

非晶質化誘導温度での熱処理又は同一エネルギー条件での機械エネルギー処理はいずれも可能である。非晶質化に要する処理時間は、熱処理の場合、通常２０分ないし１２０分、好ましくは３０分ないし９０分が、又、機械エネルギー処理の場合、通常１分ないし２０分、好ましくは３分ないし１０分が、品質コントロール、均一性、省エネルギーの面から好ましい。

加熱処理の場合は上記の通常の加熱処理の他に高周波加熱処理も使用できる。

本発明における高周波加熱としては、高周波誘電加熱、高周波誘導加熱、プラズマ加熱等のいずれでもよいが、特に高周波誘電加熱が好ましい。

周波数帯は加熱する被加熱体に依存して選択することが可能で、特にマイクロ波帯を用いるマイクロ波加熱が好ましい。マイクロ波加熱の使用周波数は、電波法でＩＳＭ（Industrial, Scientific and Medical）周波数として割り当てられている４周波数、すなわち９１５、２４５０、５８００、２２１２５ＭＨｚを使用することができる。一般的には、９１５又は２４５０ＭＨｚの周波数を使用できる。

マイクロ波加熱の方法については、オーブン方式（電子レンジ方式、コンベア式）、導波管方式のいづれでも被加熱物の形状により選択することができる。

高周波加熱の場合においては非晶質化誘導剤は必須成分ではなく、他の２成分（１）難溶性薬物と（３）非晶質安定化剤の配合種類及び比率は、使用される難溶性薬物の種類により適宜選定されるが、通常重量比で、（１）：（３）＝１：（０．１－１０）であり、好ましくは、（１）：（３）＝１：（０．３－８）、さらに好ましくは、（１）：（３）＝１：（０．５－５）である。

この場合、難溶性薬物の固体分散体は、（１）難溶性薬物と（３）非晶質安定化剤を、湿式又は乾式にて造粒（混合）し、同時に又はその後、高周波加熱することにより得られる。

高周波加熱での非晶質化に要する処理時間は高周波出力により異なるが、バッ

チ式処理の場合で3分から40分、好ましくは5分から30分が品質コントロール、均一性等の面から好ましい。コンベア式の連続処理ではバッチ式での非晶質化必要エネルギーから計算で処理時間が決定できる。高周波加熱は通常の熱処理での所要時間に比べ短時間で均一性の高い固体分散体が得られる。

造粒（混合）方法としては、特別な手法は必要なく、万能混合機、流動造粒装置、ダッシュミル、湿式造粒機、乾式造粒機等が用いられる。又、造粒時に通常の加熱処理若しくは上述のメカノケミカル処理（例えば、ボールミル粉砕、遊星ミル処理、圧縮プレス処理、剪断ロール処理、フローコーター、ニーダー等の処理等）を行ってもよく、造粒後、棚式乾燥機、流動層乾燥機、ジャイロ乾燥機、粉体乾燥機等を用いた通常の加熱処理又は上述のメカノケミカル処理を行ってもよい。

又、熱、高周波加熱及びメカノケミカル処理を組み合わせて実施することも可能である。

本発明の難溶性薬物の非晶質化においては（1）難溶性薬物、（2）非晶質化誘導剤及び（3）非晶質安定化剤の3成分以外の成分として、水、界面活性剤、酸化防止剤、防腐剤や安定剤等を配合して非晶質化することも可能である。又、（2）非晶質化誘導剤と（3）非晶質化安定剤については、それぞれ1成分でも、2成分以上配合しても、非晶質化することが可能である。

本発明の非晶質化法により得られる固体分散体の製造方法及び固体分散体を含有する経口製剤においては、上記必須成分以外に、製剤分野で一般に用いられる賦形剤（例えば、結晶セルロース、乳糖等）、崩壊剤、滑沢剤、着色剤等を適宜添加することもできる。

発明を実施するための最良の形態

本発明の（1）難溶性薬物、（2）非晶質化誘導剤及び（3）非晶質安定化剤

の必須３成分の必要性及び加熱又はメカノケミカル処理について、又、本発明の（１）難溶性薬物と（３）非晶質安定化剤を高周波加熱することの必要性について、以下実施例を用いて説明する。

試験方法１

試料１０ｍｇを、示差走査熱量計（ＤＳＣ）を用いて、昇温速度１０℃／分で測定する。吸熱ピークの頂点温度を試料の融点とする。難溶性薬物と非晶質化誘導剤の混合物（１：１）を試料とし、ＤＳＣを用いて測定するときに観察される吸熱開始温度（ピーク立ち上がり温度）を非晶質化誘導開始温度とする。

試験方法２

結晶化度は粉末Ｘ線回折測定により測定する。難溶性薬物、非晶質化誘導剤及び非晶質安定化剤の３成分単純混合試料の粉末Ｘ線回折測定を行い難溶性薬物の結晶に由来する回折角度２θにおける回折強度（Ｓ0）を読みとる。又、同様に加熱処理等を実施した試料での難溶性薬物の回折強度（Ｓ1）を読みとり、横軸にＳ0、縦軸にＳ1を対応する結晶ピークごとにプロットする。原点を通る回帰直線にて近似してその傾きの１００倍をもって結晶化度（％）とする。例えば結晶化度が変化しない場合、すなわち１００％の場合、回帰直線の仰角が４５°となり傾きが１となる。結晶化度１０％の場合、傾きは０．１となる。

実施例１

ニフェジピン１０ｇ、コハク酸１０ｇ及びＨＰＭＣ－ＡＳ２０ｇの混合物に水５ｇを加え湿式造粒し、１６０℃で１時間加熱して固体分散体を得た。この固体分散体は、ニフェジピンの結晶性ピークは認められなかった。これを常法により、顆粒とした。融点は、ニフェジピンが１７５℃、コハク酸が１９２℃、ニフェジピンとコハク酸の混合物は１６７℃であり、非晶質化誘導開始温度は１５８℃であった。

実施例２

塩酸ニカルジピン１５０ｇ、尿素１００ｇ及びヒドロキシプロピルメチルセルロース（ＨＭＰＣ）１５０ｇの混合物を、常圧下、棚式乾燥機にて１１５℃で１時間熱処理して固体分散体を得た。この固体分散体は、塩酸ニカルジピンの結晶性ピークは認められなかった。

融点は、塩酸ニカルジピンが１７０℃、尿素が１３７℃、塩酸ニカルジピンと尿素の混合物が１２９℃であり、非晶質化誘導開始温度は１１５℃であった。

この固体分散体３００ｇに対し結晶セルロース１００ｇ、乳糖１００ｇを加え、常法により乾式造粒した後、打錠にて固形錠剤を得た。

実施例３

塩酸ニカルジピン３ｇ、尿素１．５ｇ及びＨＰＭＣ５．５ｇの混合物を高速遊星ミルを用い、１００Ｇにて３分間処理した。粉末Ｘ線回折測定の結果、結晶性ピークは認められなかった。

実施例４

実施例１の１６０℃、１時間の加熱処理に代えて、マイクロウェーブ乾燥機（周波数２４５０ＭＨｚ）を用いて、２０分間（７００Ｗ）マイクロ波による加熱を行い、固体分散体を得た。この固体分散体は、ニフェジピンの結晶性ピークは認められず、非晶質であった。

実施例５

塩酸ニカルジピン２０ｇとヒドロキシプロピルメチルセルロースアセテートサクシネート（ＨＰＭＣ－ＡＳ）４０ｇに水２０ｇを加え、湿式造粒し、マイクロウェーブ乾燥機（周波数２４５０ｋＨｚ）を用いて１５分間（７００Ｗ）マイクロ波加熱を行い、固体分散体を得た。この固体分散体は、塩酸ニカルジピンの結晶性ピークは認められなかった。

この固体分散体５０ｇに対し結晶セルロース５０ｇ、乳糖５０ｇを加え、常法により乾式造粒した後、打錠にて固形錠剤を得た。

実施例６

トルブタミド３ｇとヒドロキシプロピルメチルセルロースアセテートサクシネート（ＨＰＭＣ－ＡＳ）６ｇに水５ｇを加え、乳鉢で混合し、マイクロウェーブ乾燥機（周波数２４５０ｋＨｚ）を用いて２０分間（５００Ｗ）マイクロ波加熱を行い、固体分散体を得た。この固体分散体は、トルブタミドの結晶性ピークは認められなかった。

実施例７

テオフィリン５ｇ、コハク酸２ｇ及びポリビニルピロリドン１５ｇを乾式増粒し、マイクロウェーブ乾燥機（周波数２４５０ｋＨｚ）を用いて２０分間（５００Ｗ）マイクロ波加熱を行い、固体分散体を得た。この固体分散体は、テオフィリンの結晶性ピークは認められなかった。

比較例１

実施例１において、次のいずれかのみを変化させて実施例１と全く同様に実施した。

１－Ａ：コハク酸（非晶質化誘導剤）のみを除いたもの。

１－Ｂ：ＨＰＭＣ－ＡＳ（非晶質安定化剤）のみを除いたもの。

１－Ｃ：１４０℃（非晶質化誘導開始温度１５８℃より低い温度）で熱処理したもの。

いずれの場合も完全に非晶質化しておらず、完全な固体分散体ではなかった。

ニフェジピンの結晶化度

実施例１　　：結晶性ピークは認められなかった。

比較例１－Ａ：　５０％

比較例１－Ｂ：ニフェジピンとは異なる粉末Ｘ線回折ピークが認められた。

比較例１－Ｃ：１００％

比較例２

実施例２において、次のいずれかのみを変化させて実施例２と全く同様に実施した。

２－Ａ：尿素（非晶質化誘導剤）のみを除いたもの。

２－Ｂ：ＨＰＭＣ（非晶質安定化剤）のみを除いたもの。

２－Ｃ：１００℃（非晶質化誘導開始温度１１５℃より低い温度）で熱処理したもの。

いずれの場合も完全に非晶質化しておらず、完全な固体分散体ではなかった。

塩酸ニカルジピンの結晶化度

実施例２　　：結晶性ピークは認められなかった。

比較例２－Ａ：　８５％

比較例２－Ｂ：塩酸ニカルジピンとは異なる粉末Ｘ線回折ピークが認められた。

比較例２－Ｃ：　９５％

比較例３

実施例３において、尿素（非晶質化誘導剤）のみを除いて試験を行ったが、粉末Ｘ線回折の結果、結晶化度は８０％であった。

比較例４

実施例５のマイクロ波加熱に代えて、棚式乾燥機にて１１５℃、１時間の加熱処理を行う他は実施例２と全く同様に実施した。

塩酸ニカルジピンの結晶化度は、７０％であり、完全な固体分散体ではなかった。

産業上の利用可能性

本発明は、上記のように構成されているため、難溶性薬物を非晶質化状態の固体分散体として製造でき、難溶性薬物の溶解性や吸収性を改善させることにより生物学的利用能を高めることが、期待できる。

請 求 の 範 囲

1. 難溶性薬物と非晶質化誘導剤及び非晶質安定化剤とを、加熱又はメカノケミカル処理することを特徴とする難溶性薬物の固体分散体の製造方法。

2. 加熱が高周波加熱である請求項1記載の製造方法。

3. 難溶性薬物と非晶質安定化剤を、高周波加熱することを特徴とする難溶性薬物の固体分散体の製造方法。

4. 非晶質化誘導剤が、アミノ酸若しくはその塩、アスパラテーム、エリソルビン酸若しくはその塩、アスコルビン酸若しくはその塩、ステアリン酸エステル、アミノエチルスルホン酸、イノシトール、エチル尿素、クエン酸若しくはその塩、グリチルリチン酸若しくはその塩、グルコン酸若しくはその塩、クレアチニン、サリチル酸若しくはその塩、酒石酸若しくはその塩、コハク酸若しくはその塩、酢酸カルシウム、サッカリンナトリウム、水酸化アルミニウム、ソルビン酸若しくはその塩、デヒドロ酢酸若しくはその塩、チオリンゴ酸ナトリウム、ニコチン酸アミド、尿素、フマル酸若しくはその塩、マクロゴール類、マルトース、マルトール、マレイン酸、マンニトール、メグルミン、デスオキシコール酸ナトリウム又はホスファチジルコリンである請求項1記載の製造方法。

5. 非晶質安定化剤が、セルロース誘導体、ポリビニルピロリドン、架橋ポリビニルピロリドン、ポリビニルアルコール、ポリ酢酸ビニル、ビニルアルコール・酢酸ビニルコポリマー、エチレン・酢酸ビニルコポリマー、ポリエチレンオキサイド誘導体、ポリスチレンスルホン酸ナトリウム、ゼラチン、可溶性デンプン、プルラン、デキストラン、アラビアゴム、コンドロイチン硫酸もしくはそのNa塩、ヒアルロン酸、ペクチン、キチン、キトサン、α、β若しくはγ－シクロデキストリン、アルギン酸誘導体、アクリル樹脂類、ポリビニルアセタールジエチルアミノアセテート、二酸化ケイ素又は水酸化アルミニウムである請求項1

記載の製造方法。

6. 非晶質安定化剤が、セルロース誘導体、ポリビニルピロリドン、架橋ポリビニルピロリドン、ポリビニルアルコール、ポリ酢酸ビニル、ビニルアルコール・酢酸ビニルコポリマー、エチレン・酢酸ビニルコポリマー、ポリエチレンオキサイド誘導体、ポリスチレンスルホン酸ナトリウム、ゼラチン、可溶性デンプン、プルラン、デキストラン、アラビアゴム、コンドロイチン硫酸もしくはそのNa塩、ヒアルロン酸、ペクチン、キチン、キトサン、α、β若しくはγ－シクロデキストリン、アルギン酸誘導体、アクリル樹脂類、ポリビニルアセタール、ジエチルアミノアセテート、二酸化ケイ素又は水酸化アルミニウムである請求項3記載の製造方法。

7. 請求項1ないし6 項のいずれか一つに記載の製造方法により得られる難溶性薬物の固体分散体を含有することを特徴とする製剤。

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP96/02246

A. CLASSIFICATION OF SUBJECT MATTER
Int. Cl^6 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int. Cl^6 A61K9/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP, 5-306225, A (Taiyo Pharmaceutical Industry Co., Ltd.), November 19, 1993 (19. 11. 93)(Family: none)	1 - 7
A	JP, 2-67229, A (Nisshin Flour Milling Co., Ltd.), March 7, 1990 (07. 03. 90)(Family: none)	1 - 7
A	JP, 63-115815, A (Mitsubishi Kasei Corp.), May 20, 1988 (20. 05. 88) & WO, 88/03023, A	1 - 7

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
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Date of the actual completion of the international search	Date of mailing of the international search report
November 1, 1996 (01. 11. 96)	November 12, 1996 (12. 11. 96)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

国際調査報告

国際出願番号 PCT／JP96／02246

A. 発明の属する分野の分類（国際特許分類（IPC））

IntCl' A61K9／00

B. 調査を行った分野

調査を行った最小限資料（国際特許分類（IPC））

IntCl' A61K9／00

最小限資料以外の資料で調査を行った分野に含まれるもの

国際調査で使用した電子データベース（データベースの名称、調査に使用した用語）

C. 関連すると認められる文献

引用文献のカテゴリー＊	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する請求の範囲の番号
A	JP、5－306225、A（大洋薬品工業株式会社）19. 11月. 1993（19. 11. 93） （ファミリーなし）	1－7
A	JP、2－67229、A（日清製粉株式会社）7. 3月. 1990（07. 03. 90） （ファミリーなし）	1－7
A	JP、63－115815、A（三菱化成工業株式会社）20. 5月、1988（20. 05. 88） &WO、88／03023、A	1－7

☐ C欄の続きにも文献が列挙されている。

☐ パテントファミリーに関する別紙を参照。

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「O」口頭による開示、使用、展示等に言及する文献
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「T」国際出願日又は優先日後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの
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「&」同一パテントファミリー文献

国際調査を完了した日	国際調査報告の発送日
01. 11. 96	12.11.96

国際調査機関の名称及びあて先	特許庁審査官（権限のある職員）	4C	7329
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World Intellectual Property Organization International Bureau

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(81) Designated Countries:

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Appended Disclosure Documents: International Investigation Report

(54) Title of Invention:

A method for making a medicine which is hard to dissolve amorphous (non-crystalline)

(57) Abstract:

A method for manufacturing a solid dispersoid of a medicine which is hard to dissolve which is characterized by the heating the hardly soluble medicine, an amorphism (non-crystallization) inducing agent and an amorphism (non-crystallization) stabilizer or the mechanochemical treatment of the same; and a method for manufacturing a solid dispersoid of a medicine which is hard to dissolve which is characterized by the high-frequency heating of the medicine which is hard to dissolve and an amorphism stabilizer. These processes make it possible to make medicines which are hard to dissolve amorphous at a temperature lower than those employed in the conventional methods. The solid dispersoids of the amorphous medicines which are hard to dissolve obtained by these methods have an improved absorption rate from the mucous membranes and the rectum, which makes it possible to raise their bioavailability.

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Code employed for the purpose of identifying the countries adhering to the PCT on the first page of the pamphlet of the international application which is disclosed based on the PCT

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Specification

A method for making a medicine which is hard to dissolve amorphous (non-crystalline)

Technical Field

The invention in question concerns a method for manufacturing a solid dispersoid by relying on a technique in which a medicine which is hard to dissolve is used effectively, and in particular a method for making such a medicine amorphous. This technique will be used in fields in which the quality of the elution of medicine is a problem, for example, in the fields of agricultural chemicals and medicines, perfumes and cosmetics, and the medical treatment, and in particular in the field of medical treatment.

Background Technique

In the design of formulations for internal use, the raising of bioavailability by improving the solubility and the absorbability of medicines which are difficult to dissolve is important from the standpoint of the effectiveness and safety of the said medicines.

As means for increasing the bioavailability of a medicine which is difficult to dissolve, there are methods from improving the solubility of the medicine by such things as the atomization and wetting of the medicine's particles and an improvement of its solubility, the creation of a solid dispersoid, the use of polymorphs, etc., but the use of polymorphs, etc., but the method which has the focus of attention in particular is the method whereby a solid dispersoid is manufactured by a method in which the medicine is made amorphous. The term a "solid dispersoid" stands for a dispersoid which has been kept in a state in which the medicine has been made completely amorphous, being something in which the medicine has been dispersed in a carrier in a monomolecular state. In general the non-crystalline form is in a high energy state compared to the crystal form, and is something for which a high degree of solubility can be anticipated.

The methods for manufacturing a solid dispersoid are broadly classified as the solvent method, the fusion method (the heating method), the fusion-solvent method, the mechanochemical method, and other.

The solvent method is a method whereby a solid dispersoid is obtained by the elimination/gas diffusion of the solvent in the presence of nuclear particles or in that state after both the medicine and the water soluble macromolecular base, which is a non-crystalline stabilization agent, have been dissolved in an organic solvent. This method suffers from the deficiencies that the costs of manufacture are high, and in addition that cases in which residual solvent for the medicine are concern can be observed given the fact that a large quantity of organic solvent is used, even though it is a method which is superior as a method for improving the solubility of a medicine which is hard to dissolve.

As for the fusion method (the heating method), this is a method involving the lowering of the melting point of a mixture of the medicine and the water soluble macromolecular base, which is the non-crystalline stabilization agent, the heating and kneading of the mixture at a temperature below the melting point of both its components, the dispersion of the medicine in a molecular state, and its cooling, caking and pulverization.

The fusion method is superior insofar as it does not involve the use of organic solvents. However, depending on the type of the medicine which is hard to dissolve, there are times when it is not possible to achieve the creation of an adequate amorphous (non-crystalline) state by only adding a non-crystallizing stabilizer as the carrier used for the fixed **[Translator: There may be mistake here, and this might possibly read "solid", since one character appears to be wrong.]** dispersoid.

In addition, in order to transform the medicine completely into an amorphous (non-crystalline) state, the process is conducted below the melting points of the medicine and the carrier used for the fixed **[Translator: Same as in the preceding paragraph.]** dispersoid, but it is necessary to carry out the kneading treatment at a high temperature, so one finds not only cases in which the medicine is degraded, the carrier deteriorates, etc., but also instances arise in which the non-crystallization process is insufficient.

For example, in the method in which only the medicine which is hard to dissolve and the water soluble macromolecular base, which is the amorphous stabilization agent, are employed, and heating and fusion of the two is conducted by employing a lowering of their melting points, the lowering of the melting point is at best 10 degrees Centigrade, perhaps solely so since the temperature of the thermal treatment becomes a high, or since it is common for the macromolecular base to be amorphous from the start, the apparent melt viscosity is high and the microdispersibility of the medicine and the water soluble macromolecules is poor, so there are times when it is not possible to achieve adequate non-crystallization depending on the medicine involved.

In addition, there have also been attempts at heating and fusion with medicines which are hard to dissolve by using as the carrier used for solid dispersoids not a water soluble macromolecular base but rather low molecular chemical compounds such as phosphatidylcholine, etc., as non-crystallization inducers. However, there are concerns that decomposition and reformation of the medicine will occur as a result of the heating treatment. Moreover, in the event that the temperature of the products treated by heating is lowered to room temperature, it proves difficult to maintain the amorphous state which has been achieved so there are concerns that the stability will be poor.

The mechanochemical method is a method in which a solid dispersoid is obtained by improving the promotion of the non-crystallization of the medicine solid and the promotion of the dispersion of the medicine which has been made amorphous (non-crystalline) to the carrier by employing mechanical energy such as compression, shearing, friction, etc. Concretely, there are such treatments as ball mill mixed grinding, planetary mill treatment, compression press treatment, shear roll mixed treatment, etc.

With the mechanochemical method, there are cases in which special machinery is necessary since (perhaps because the level of the mechanical energy is low) it is difficult to transform the medicine into an amorphous state solely by this means even in the event that an amorphous stabilization agent is added to the medicine which is hard to dissolve (Patent Disclosure Bulletin 4-818106).

As can be seen from the above, methods have been sought whereby it possible to obtain in an industrially inexpensive manner a solid dispersoid in a completely amorphous state at a price which is more inexpensive than previous methods.

Disclosure of the Invention

As a result of diligent examination in order to surmount the problems which remain in these prior methods, the inventors discovered a method for making a medicine which is hard to dissolve amorphous which is characterized by the fact that 3 components, namely (1) the medicine which is hard to dissolve; (2) an amorphism inducing agent; and (3) an amorphism stabilization agent are mixed together, and heating or mechanochemical treatment is then carried out on the mixture. In addition, they further discovered that high frequency heating is preferable to ordinary heater heating and steam heating as a heating treatment.

In addition, they discovered a method for making a medicine which is hard to dissolve amorphous which is characterized by the fact that components, namely (1) the medicine which is hard to dissolve; and (3) an amorphism stabilization agent are mixed together, and high frequency heating treatment is then carried out on the mixture.

Furthermore, it is also possible to manufacture a formulation of the medicine which is hard to dissolve which has employed the solid dispersoid obtained by means of the non-crystallization method which constitutes the invention in question.

The (1) medicine which is hard to dissolve in the invention in question is a medicine whose solubility in water is extremely low and whose absorption from the intestinal tract, the mucous membrane of the nose, the rectum, etc. is poor, a medicine for which an improvement of the absorption is difficult by the making of ordinary formulations, and a medicine for which the absorption can be raised by means of non-crystallization. For example, one can mention such examples as the chemical compounds of the dihydropyridine family such as nifedipine, nicardipine hydrochloride, phenacetin, digitoxin, diazepam, phenytoin, tolbutamide, theophyline, griseofulvin, chloramphenicol, etc.

As for the (2) amorphism inducing agent in the invention in question, it is acceptable if it is a chemical compound whereby the mixture between it and the medicine causes a lowering of the latter's melting point, and a crystalline chemical compound is particular desirable. This is a chemical compound which causes a transformation of the crystal lattice energy of the medicine which is hard to dissolve in a low energy direction, and moreover which possesses the function and property of increasing the fluctuations of the crystal lattice as the same temperature. The amorphism inducing agent which is selected differs in accordance with the kind of medicine which is hard to dissolve; for

example, in the event that an (a) basic medicine which is hard to dissolve is selected, then the selection of a neutral substance or an acidic substance, and an acidic substance in particular, is desirable, and in the event a (b) acidic medicine which is hard to dissolve is selected, then the selection of a neutral substance or an basic substance, and an basic substance in particular, is desirable.

Concretely, one can mention the following as examples of amorphism inducing agents: amino acids or their salts (aspartic acid and its Na salt, Mg salt, etc., glycine, alanine, glutamic acids and glutamic acid hydrochloride, etc.), asparatame, erythorbic acid and its salts (Na salt, etc.), ascorbic acid and its salts (Na salt, etc.), stearic acid ester, aminoethyl sulfonic acid, inositol, ethylurea, citric acid and its salts (salts like 3-Na, 2-Na, dihydrogen Na, Ca salt, etc.), glycyrrhetic acid and its salts (Na salts like 3-Na, 2-Na, etc., ammonium salts like diammonium, monoammonium, etc., K salt), gluconic acid and its salts (Na salt, Ca salt, Mg salt, etc.), creatinine, salicylic acid and its salts (Na salts, etc.), tartaric acid and its salts (Na salt, K-Na salt, hydrogen-K salt, etc.), succinic acid and its salts (Na salts such as 2-Na, 1-Na, etc.), calcium acetate, saccharin sodium, aluminum hydroxide, sorbic acid and its salts (K salts, etc.), dehydroacetic acid and its salts (Na salt, etc.), thiomalic acid sodium **[sic]**, nicotinic acid amide, urea, fumaric acid and its salts (Na salt, etc.), the Macrogol group, maltose, maltol, maleic acid, mannitol, meglumine, desoxylcholic acid sodium, phosphatidyl choline, etc.

Preferably, one can mention as the following as examples of the amorphism inducing agent: amino acids or their salts (aspartic acid and its Na salt, Mg salt, etc., glycine, alanine, glutamic acids and glutamic acid hydrochloride, etc.), ascorbic acid and its salts (Na salt, etc.), stearic acid ester, aminoethyl sulfonic acid, ethylurea, citric acid and its salts (salts like 3-Na, 2-Na, dihydrogen Na, Ca salt, etc.), glycyrrhetic acid and its salts (Na salts like 3-Na, 2-Na, etc., ammonium salts like diammonium, monoammonium, etc., K salt), creatinine, tartaric acid and its salts (Na salt, K-Na salt, hydrogen-K salt, etc.), succinic acid and its salts (Na salts such as 2-Na, 1-Na, etc.), urea, fumaric acid and its salts (Na salt, etc.), the Macrogol group, maltose, maltol, mannitol, meglumine, etc.

More preferably, one can mention as the following as examples of the amorphism inducing agent: amino acids or their salts (aspartic acid and its Na salt, Mg salt, etc., glycine, alanine, glutamic acids and glutamic acid hydrochloride, etc.), ethylurea, glycyrrhetic acid and its salts (Na salts like 3-Na, 2-Na, etc., ammonium salts like diammonium, monoammonium, etc., K salt), tartaric acid and its salts (Na salt, K-Na salt, hydrogen-K salt, etc.), succinic acid and its salts (Na salts such as 2-Na, 1-Na, etc.), urea, the Macrogol group, maltose, maltol, mannitol, meglumine, etc.

Still more preferably, one can mention as the following as examples of the amorphism inducing agent: glycyrrhetic acid and its salts (Na salts like 3-Na, 2-Na, etc., ammonium salts like diammonium, monoammonium, etc., K salt), succinic acid and its salts (Na salts such as 2-Na, 1-Na, etc.), urea, maltol, mannitol, etc.

In addition, the lowering of the melting point of the amorphism inducing and the medicine which is hard to dissolve differs depending on the combination with the medicine which is hard to dissolve, but one can preferably use a chemical compound

which lowers the melting point by 5 degrees Centigrade or more than the melting point of the medicine which is hard to dissolve.

Still more preferably, one can use a chemical compound which lowers the melting point of the mixture of amorphism inducing agent and the medicine which is hard to dissolve by 15 degrees Centigrade or more than the melting point of the medicine which is hard to dissolve, and most preferably of all one can use a chemical compound which lowers the former melting point by 25 degrees Centigrade or more than the latter.

In the event that the heating used is high frequency heating, it is possible to make the medicine which is hard to dissolve amorphous by high frequency heating of a mixture of only the medicine which is hard to dissolve and an amorphism stabilizer without employing a amorphism inducing agent. Naturally, high frequency of 3 components in which an amorphism inducing agent has been mixed also provides a full effect.

After the crystal structure of the medicine which is hard to dissolve has been caused to fluctuate by the amorphism inducing agent, the amorphism stabilizer stabilizes the amorphous state by the interaction of its crystal lattice on the fluctuating state.

Therefore, if it is an amorphism stabilizer which possesses the above-mentioned activity it is possible to use this stabilizer in the invention in question. In other words, it is acceptable to use anything for an amorphism stabilizer provided that it is a chemical compound that preserves the functional group which possesses an interaction with the medicine which is hard to dissolve, but it is preferable to use a chemical compound whose solubility with the medicine which is hard to dissolve is great, which possesses a flexible functional group, and which has a high degree of thermal stability, for example, the amorphous macromolecular bases listed below. The phrase "a chemical compound whose solubility with the medicine which is hard to dissolve is great" refers to a chemical compound for which the values of the solubility parameters (Solubility Parameter: Encyclopedia of Polymer Science and Engineering, volume 15, page 393, John Wiley and Sons, Inc., 1989) are close. Still more preferable is a chemical compound in which the amorphism stabilizer has a solubility which is highly compatible with not the medicine which is hard to dissolve but also the amorphism inducing agent.

In addition, the functional group of the interacting amorphism stabilizer which is selected differs in accordance with the type of medicine which is hard to dissolve, so in the event that an (a) basic medicine which is hard to dissolve is selected, then the selection of a neutral substance or an acidic substance, and an acidic substance in particular, is desirable, and in the event a (b) acidic medicine which is hard to dissolve is selected, then the selection of a neutral substance or an basic substance, and an basic substance in particular, is desirable.

In the invention in question, one can mention the following as examples of the (3) amorphism stabilizer: cellulose inducers (for example, hydroxyethylcellulose, hydroxypropylmethylcellulose (HPMC), hydroxypropylmethylcellulose – acetate succinate (HPMC – AS), methylcellulose, ethylcellulose, carboxymethylcellulose, cellulose acetate phthalate, etc.), polyvinylpyrrolidone, crosslinked polyvinylpyrrolidone,

polyvinyl alcohol, polyvinyl acetate, vinyl alcohol – vinyl acetate copolymer, ethylene – vinyl acetate copolymer, polyethylene oxide inducers (for example, polyethylene glycol, polyoxyethylene polyoxypropylene cetyl ether, polyoxyethylene alkyl ether, polyoxyethylene oxyphenyl ether, polyoxyethylene oleyl amine, polyoxyethylene oleyl ether, polyoxyethylene oleyl ether sodium phosphate, polyoxyethylene hardened castor oil, polyoxyethylene stearyl ether, polyoxyethylene stearyl ether phosphate, polyoxyethylene cetyl ether, polyoxyethylene cetyl ether sodium phosphate, polyoxyethylene sorbit beeswax, polyoxyethylene nonylphenyl ether, polyoxyethylene castor oil, polyoxyethylene behenyl ether, polyoxyethylene polyoxypropylene glycol, polyoxyethylene polyoxypropylene cetyl ether, polyoxyethylene lauryl ether, polyoxyethylene lanolin, polysorbate 40, polysorbate 60, polysorbate 65, polysorbate 80, etc.), polystyrene sodium sulfonate, gelatin, soluble starch, Pullulan, dextran, gum arabic, chondroitin sulfate and its Na salts, hyaluronic acid, pectin, chitin, chitosan, alpha-, beta-, or gamma – cylcodextrine, alginic acid inducers (for example, methacrylic acid inducers like alginic acid and its Na salts and propylene glycol ether, etc.), the acrylic resin family (methacrylic acid, methyl methacrylate, butyl methacrylate, dimethylaminoethyl methacrylate, trimethyl ammonium ethyl chloride methacrylate, acrylic acid, ethyl acrylate, etc.. and/or the homopolymers and copolymers of acrylic acid inducers such as amino alkyl – methacrylate copolymer, methyl methacrylate – methacrylic acid copolymer, methacrylic acid – ethyl acrylate copolymer, methacrylic acid – n-butyl acrylate copolymer, acrylic ester – vinyl acetate copolymer, 2-ethylhexyl acrylate – vinyl pyrrolidone copolymer, starch acrylate, etc.), and polyvinyl acetol diethylaminoacetate, etc.

In addition, it is also possible to use chemical compounds possessing a gel formation capability, such as silicon dioxide, aluminium hydroxide, etc., as the amorphism stabilizer of the invention in question.

Preferably, one can mention as the following as examples of the amorphism stabilizer: hydroxyethylcellulose, hydroxypropylmethylcellulose (HPMC), hydroxypropylmethylcellulose – acetate succinate (HPMC – AS), polyvinylpyrrolidone, polystyrene sodium sulfonate, alpha-, beta-, or gamma – cylcodextrine, the acrylic resin family (methacrylic acid, methyl methacrylate, butyl methacrylate, dimethylaminoethyl methacrylate, trimethyl ammonium ethyl chloride methacrylate, acrylic acid, ethyl acrylate, etc.. and/or the homopolymers and copolymers of acrylic acid inducers, etc.), and polyvinyl acetol diethylaminoacetate, etc.

More preferably, one can mention as the following as examples of the amorphism stabilizer: hydroxypropylmethylcellulose (HPMC), hydroxypropylmethylcellulose – acetate succinate (HPMC – AS), polyvinylpyrrolidone, the acrylic resin family (methacrylic acid, methyl methacrylate, butyl methacrylate, dimethylaminoethyl methacrylate, trimethyl ammonium ethyl chloride methacrylate, acrylic acid, ethyl acrylate, etc. and/or the homopolymers and copolymers of acrylic acid inducers, etc.), and polyvinyl acetol diethylaminoacetate, etc.

The types and ratios of the combination of the (1) the medicine which is hard to dissolve; (2) an amorphism inducing agent; and (3) an amorphism stabilizer are selected appropriately in accordance with the type of medicine which is hard to dissolve, but the

usual ratio by weight is as follows: (1) : (2) : (3) = 1 : (0.1 – 10) : (0.1 – 10), with a ratio of (1) : (2) : (3) = 1 : (0.3 – 3) : (0.3 – 8) being preferable, and a ratio of (1) : (2) : (3) = 1 : (0.3 – 2) : (0.5 – 5) being still more preferable.

As for the solid dispersoid of the medicine which is hard to dissolve, first the three necessary components, (1) the medicine which is hard to dissolve; (2) an amorphism inducing agent; and (3) an amorphism stabilizer, are granulated (mixed) in a wet or dry manner, and at the same time as or after the mixing of this mixture the solid dispersoid is obtained by either thermal treatment at a temperature higher than that at which the induction of amorphism starts and moreover at a temperature at which the medicine which is hard to dissolve will not be degraded and deteriorate, or mechanochemical treatment under the same energy conditions as this heating treatment. It is preferable that the heating temperature of the mixture at this time be set at a level below the melting point of the medicine which is hard to dissolve, and also preferable that the temperature be as close as possible to the temperature at which the induction of amorphism starts. If the heating temperature is lower than the temperature at which the induction of amorphism starts by for example 5 to 10 degrees Centigrade, the non-crystallation process will not proceed fully.

The meaning of the phrase "a temperature at which the induction of amorphism starts" refers to the temperature at the start of endothermy (the temperature of the start of the peak) which is observed when one measures a rise in temperature of 10 degrees Centigrade per minute using a Differential Scanning Calorimeter (DSC) for 10 mg of the mixture sample (1 : 1) of the medicine which is hard to dissolve and the amorphism inducing agent.

As for the methods for granulation, there is no need for a special method; rather, a universal mixing machine, a flow granulation device, a dash mill, a wet granulation machine, a dry granulation machine, etc., are used. Moreover, it is acceptable to carry out thermal treatment at the time of granulation, and after granulation it is acceptable to conduct non-crystallization by carrying out heating treatment with, for example, a plate-style drying machine, a fluidized drying machine, a gyro drying machine, a powder drying machine, etc., by such heating methods as heating by an ordinary heater, steam heating, infrared heating, far infrared heating, etc.

Moreover, it is possible to carry out non-crystallization by employing not only heat but also mechanochemical treatment based on such forms of mechanical energy as compression, shearing, friction, etc. For example, it is possible to carry out non-crystallization by employing only mechanochemical treatment by such treatments as ball mill powderizing, planetary mill treatment, compression press treatment, shearing roll treatment, a kneader, etc. without any heating of the above-mentioned 3 components. By relying on these methods, it is possible to carry out non-crystallization for medicines which are unstable in relation to heat.

In addition, it is also possible to employ the vibrating energy of ultrasonic waves, etc., and electromagnetic energy treatments such as electrical fields, magnetism, etc., as the energy for creating a state of flux in the crystal lattice in the medicine which is hard to dissolve among the 3 components of the mixture.

Either thermal treatment at the temperature of amorphism induction or mechanical energy treatment under the same conditions is acceptable. As far as the treatment time for non-crystallization is concerned, it is preferable from the standpoint of quality control, uniformity, and energy conservation that this usually be between 20 and 120 minutes, and preferably between 30 and 90 minutes, in the case of thermal treatment, and usually between 1 and 20 minutes, and preferably between 3 and 10 minutes, in the case of mechanical energy treatment.

In the event of heating treatment, it is also possible to use high frequency wave heating treatment in additional to the above-mentioned usual heating treatments.

It is possible to select the frequency band to be used in accordance with the bodies to be heated, and microwave heating employing the microwave band is particularly desirable. It is possible to use as the frequencies for microwave heating the 4 frequencies allotted as ISM (Industrial, Scientific, and Medical) frequencies by the Wireless Telegraphy Act, namely 915, 2450, 5800, and 22125 MHz. In general the 915 and 2450 frequencies are used.

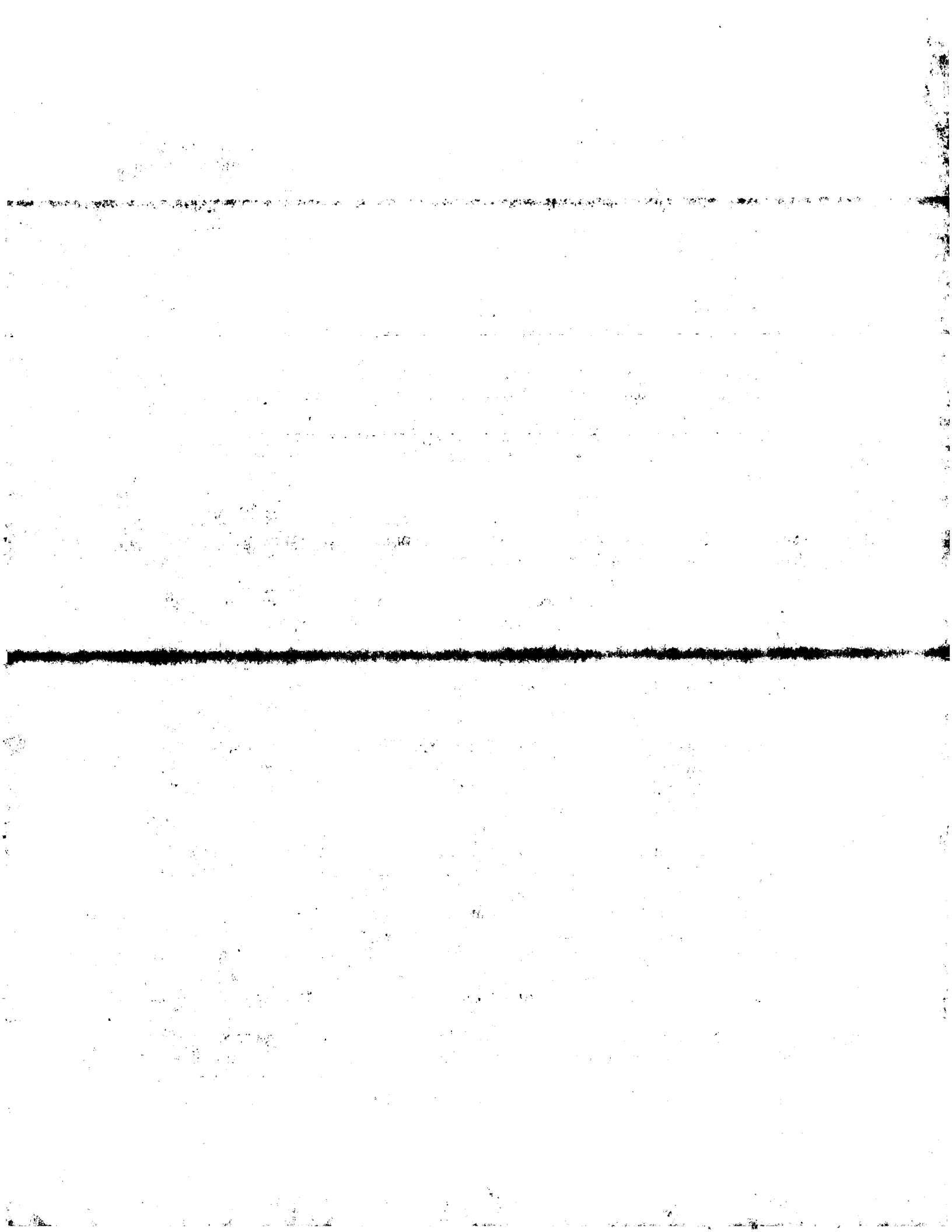
As far as the method of the microwave heating is concerned, it is possible to select either the oven style (microwave oven, conveyor style) or the wave guide style depending on the shape of the item to be heated.

In the event of high frequency wave heating, the amorphism induction agent is not a necessary component, and the types and ratios of the combination of the (1) the medicine which is hard to dissolve (3) an amorphism stabilizer are selected appropriately in accordance with the type of medicine which is hard to dissolve, but the usual ratio by weight is as follows: (1) : (3) = 1 : (0.1 – 10), with a ratio of (1) : (3) = 1 : (0.3 – 8) being preferable, and a ratio of (1) : (3) = 1 : (0.5 – 5) being still more preferable.

In this case, the solid dispersoid of the medicine which is hard to dissolve is obtained by first granulating (mixing)(1) the medicine which is hard to dissolve and (3) an amorphism stabilizer in a wet or dry manner, and at the same time as or after the mixing of this mixture high frequency wave heating is carried out.

The treatment time required for non-crystallization by high frequency wave heating depends on the output of the high frequency waves, but it is preferable from the standpoint of quality control, uniformity, etc. that this usually be between 3 and 40 minutes, and preferably between 5 and 30 minutes, in the case of batch treatment. In the case of continuous conveyor-style treatment, it is possible to determine the treatment time by calculating based on the energy required for non-crystallization in the batch treatment. With high frequency wave heating one can obtain a solid dispersoid with a high degree of uniformity in a short time compared to the time required by ordinary thermal treatments.

As for the methods for granulation (mixing), there is no need for a special method; rather, a universal mixing machine, a flow granulation device, a dash mill, a wet granulation machine, a dry granulation machine, etc., are used. Moreover, it is acceptable to carry out ordinary thermal treatment or the mechanochemical treatments described



above (for example, ball mill powderizing, planetary mill treatment, compression press treatment, shearing roll treatment, a flow coater, a kneader, etc.) at the time of granulation, and after granulation it is acceptable to conduct out ordinary thermal treatment or the mechanochemical treatments described above by carrying out heating treatment with, for example, a plate-style drying machine, a fluidized drying machine, a gyro drying machine, a powder drying machine, etc.

In addition, it is possible to conduct thermal treatment, high frequency wave heating, and mechanochemical treatment in combination.

It is also possible to carry out non-crystallization by combining water, a surface activation agent, an anti-oxidation agent, preservatives, a stabilizer, etc., in addition to the 3 necessary components, (1) the medicine which is hard to dissolve, (2) the amorphism inducing agent, and (3) the amorphism stabilizer, in the non-crystallization of the medicine which is hard to dissolve which constitutes the invention in question. In addition it is possible to carry out crystallization by combining one component or 2 or more components for (2) the amorphism inducing agent and (3) the amorphism stabilizer, respectively.

In the method for manufacturing the solid dispersoid of a medicine which is hard to dissolve which is obtained by means of the non-crystallization method which constitutes the invention in question and the orally administered preparation which contains the solid dispersoid, it is possible to add as appropriate an excipient (for example, crystal cellulose, milk sugar, etc.), a disintegrating agent, a lubricant, a coloring agent, etc. in addition to the above-mentioned necessary components.

Optimal Form for the Implementation of the Invention

An explanation employing working examples follows below concerning the necessity of the 3 necessary components, (1) the medicine which is hard to dissolve, (2) the amorphism inducing agent, and (3) the amorphism stabilizer, and their heating or mechanochemical treatment, of the invention in question, and moreover of the necessity of the high frequency wave heating of (1) the medicine which is hard to dissolve and (3) the amorphism stabilizer.

Experimental Methods 1

10 mg of the test substance is measured with a Differential Scanning Calorimeter (DSC) at a speed of temperature increase of 10 degrees Centigrade per minute. The peak temperature of the endothermic peak is taken to be the melting point of the test substance. Taking a combination of the medicine which is hard to dissolve and the amorphism inducing agent (1 : 1) as the test material, the temperature at the start of endothermy (the temperature of the start of the peak) which is observed when one measures using a DSC is taken to be the temperature at which amorphism is induced.

Experimental Methods 2

The degree of crystallization is measured by X-ray powder diffraction measurement. Readings are taken of the strength of diffraction (S0) in the diffraction angle 2θ which originates in the medicine which is hard to dissolve after the conducting of X-ray powder diffraction measurements for a simple mixed text substance containing the 3 components, the medicine which is hard to dissolve, the amorphism inducing agent, and the amorphism stabilizer. Similarly, readings are taken of the strength of diffraction (S2) of the medicine which is hard to dissolve with the test material on which heating treatment has been carried out, and a plot is made for each crystal peak with So corresponding to the horizontal axis and S1 corresponding to the vertical axis. Approximating by the regression line which passes the point of origin, its slope is multiplied by a factor of 100 and taken to be the degree of crystallization (%). For example, in the event that the degree of crystallization does not change, in other words, in the event that it is 100%, the angle of elevation of the regression line is 45 degrees, so the slope is 1. In the event that the degree of crystallation is 10%, the slope is 0.1.

Working Example 1

5g of water were added to a mixture of 10g of nifedipine, 10g of succinic acid, and 20g of HPMC – AS and wet granulation was conducted, and a solid dispersoid was obtained after heating at 160 degrees Centigrade for 1 hour. The crystalline peak of the nifedipine could not be recognized for this solid dispersoid. This was granulated by the usual method. As far as the melting points are concerned, that of nifedipine is 175 degrees Centigrade, that of succinic acid is 192 degrees Centigrade, and that of the mixture of nifedipine and succinic acid was 167 degrees Centigrade, and the temperature at which amorphism started was 158 degrees Centigrade.

Working Example 2

A mixture of 150g of nicardepine chloride, 100g of urea, and 150g of hydroxypropylmethylcellulose (HMPC **[sic]**) was thermally treated for one hour at 115 degrees Centigrade with a plate-style drying machine under ordinary pressure and a solid dispersoid was obtained. No crystalline peak of the nicardipine chloride could be recognized for this solid dispersoid.

As far as the melting points are concerned, that of nicardipine chloride is 170 degrees Centigrade, that of urea is 137 degrees Centigrade, and that of the mixture of nicardepine chloride and urea was 129 degrees Centigrade, and the temperature at which amorphism started was 115 degrees Centigrade.

100g of crystal cellulose and 10g of milk sugar were added to 300g of this solid dispersoid and after dry granulation by the usual method solid tablets were obtained by tablet making.

Working Example 3

Using a high speed planetary mill, a mixture of 3g of nicardipine chloride, 1g of urea, and 5g of HPMC was treated for 3 minutes at 100G. The results of the X-ray powder diffraction measurements were that no crystalline peak could be recognized.

Working Example 4

Instead of the heating treatment of 1 hour at 160 degrees Centigrade as in Working Example 1, heating was carried out by microwaves (700W) for 20 minutes using a microwave drying machine (frequency 2450 MHz), and a solid dispersoid was obtained. No crystalline peak of the nifedipine could be recognized for this solid dispersoid, and it was amorphous.

Working Example 5

20g of water was added to 20g of nicardipine chloride and 40g of hydroxypropylmethylcellulose – acetate succinate (HPMC – AS), wet granulation was conducted, and heating was conducted with microwaves (700W) for 15 minutes using a microwave drying machine (frequency 2450 MHz), and a solid dispersoid was obtained thereby. No crystalline peak of the nicardipine chloride could be recognized for this solid dispersoid.

50g of crystal cellulose and 50g of milk sugar were added to 50g of this solid dispersoid, and after dry granulation by the usual method solid tablets were obtained by tablet making.

Working Example 6

5g of water was added to 3g of tolbutamide and 6g of hydroxypropylmethylcellulose – acetate succinate (HPMC – AS), the combination was mixed in a mortar, and heating was conducted with microwaves (500W) for 20 minutes using a microwave drying machine (frequency 2450 MHz), and a solid dispersoid was obtained thereby. No crystalline peak of the tolbutamide could be recognized for this solid dispersoid.

Working Example 7

5g of theophyline, 2g of succinic acid and 15g of polyvinyl pyrrolidone were dry granulated **[Translator: One wrong character in the text.]** and heating was conducted with microwaves (500W) for 20 minutes using a microwave drying machine (frequency 2450 MHz), and a solid dispersoid was obtained thereby. No crystalline peak of the theophyline could be recognized for this solid dispersoid.

Comparative Example 1

Working example 1 was carried out in exactly the same manner except that only one of the following changes was introduced.

1 – A: Only the succinic acid (the amorphism inducing agent) was omitted.

1 – B: Only the HPMC - AS (the amorphism stabilizer) was omitted.

1 – C: Thermal treatment was conducted at 140 degrees Centrigade (a temperature which is lower than 158 degrees Centigrade, which is the temperature at which the induction of amorphism starts).

There was absolutely no amorphism in any of these cases, and the product was not a complete solid dispersoid.

Degree of crystallization of the nifedipine

Working Example 1: No crystalline peak could be recognized.

1 – A: 50%

1 – B: An X-ray powder diffraction peak which is different from that of nifedipine was recognized.

1 – C: 100%

Comparative Example 2

Working example 2 was carried out in exactly the same manner except that only one of the following changes was introduced.

2 – A: Only the urea (the amorphism inducing agent) was omitted.

2 – B: Only the HPMC (the amorphism stabilizer) was omitted.

2 – C: Thermal treatment was conducted at 100 degrees Centrigade (a temperature which is lower than 115 degrees Centigrade, which is the temperature at which the induction of amorphism starts).

There was absolutely no amorphism in any of these cases, and the product was not a completely solid dispersoid.

Degree of crystallization of the nicardipine chloride

Working Example 2: No crystalline peak could be recognized.

2 – A: 85%

2 – B: An X-ray powder diffraction peak which is different from that of nicardipine chloride was recognized.

2 – C: 95%

Comparative Example 3

In Working Example 3, an experiment was conducted in which only the urea (the amorphism inducing agent) was omitted, and the results of the X-ray powder diffraction was that the degree of crystallization was 80%.

Comparative Example 4

Other than the fact that heating treatment was carried out for 1 hour at 115 degrees Centigrade by a plate-style drying machine in the place of the microwave heating in Working Example 5, everything was carried out in exactly the same manner as in Working Example 2.

The degree of crystallization of the nicardipine chloride was 70%, and the product was not a completely solid dispersoid.

Scope of Claims

1. The method for manufacturing a solid dispersoid of a medicine which is hard to dissolve which is characterized by the heating or mechanochemical treatment of the medicine which is hard to dissolve, an amorphism inducing agent, and an amorphism stabilizer.

2. The manufacturing method recorded in Claim 1 in which the heating is high frequency wave heating.

3. The method for manufacturing a solid dispersoid of a medicine which is hard to dissolve which is characterized by the high frequency wave heating of the medicine which is hard to dissolve and an amorphism stabilizer.

4. The manufacturing method recorded in Claim 1 in which the following are examples of amorphism inducing agents: amino acids or their salts, asparatame, erythorbic acid and its salts, ascorbic acid and its salts, stearic acid ester, aminoethyl sulfonic acid, inositol, ethylurea, citric acid and its salts, glycyrrhetic acid and its salts, gluconic acid and its salts, creatinine, salicylic acid and its salts, tartaric acid and its salts, succinic acid and its salts, calcium acetate, saccharin sodium, aluminum hydroxide, sorbic acid and its salts, dehydroacetic acid and its salts, thiomalic acid sodium **[sic]**, nicotinic acid amide, urea, fumaric acid and its salts, the Macrogol group, maltose, maltol, maleic acid, mannitol, meglumine, desoxylcholic acid sodium, phosphatidyl choline, etc.

5. The manufacturing method recorded in Claim 1 in which the following are examples of amorphism stabilizers: cellulose inducers, polyvinylpyrrolidone, crosslinked polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, vinyl alcohol – vinyl acetate copolymer, ethylene – vinyl acetate copolymer, polyethylene oxide inducers, polystyrene

sodium sulfonate, gelatin, soluble starch, Pullulan, dextran, gum arabic, chondroitin sulfate and its Na salts, hyaluronic acid, pectin, chitin, chitosan, alpha-, beta-, or gamma – cylcodextrine, alginic acid inducers, the acrylic resin family, polyvinyl acetol diethylaminoacetate, silicon dioxide, aluminium hydroxide, etc.

6. The manufacturing method recorded in Claim 3 in which the following are examples of amorphism stabilizers: cellulose inducers, polyvinylpyrrolidone, crosslinked polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, vinyl alcohol – vinyl acetate copolymer, ethylene – vinyl acetate copolymer, polyethylene oxide inducers, polystyrene sodium sulfonate, gelatin, soluble starch, Pullulan, dextran, gum arabic, chondroitin sulfate and its Na salts, hyaluronic acid, pectin, chitin, chitosan, alpha-, beta-, or gamma – cylcodextrine, alginic acid inducers, the acrylic resin family, polyvinyl acetol diethylaminoacetate, silicon dioxide, aluminium hydroxide, etc.

7. The preparation which is characterized by the fact that it contains a solid dispersoid of the medicine which is hard to dissolve which is obtained by means of the methods of manufacture recorded in any one of the claims from Claim 1 to Claim 6 above.